

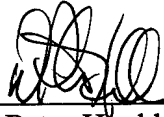
REMARKS

The claims have been amended to delete multiple dependencies, thereby reducing the overall filing cost, and to place them into proper U.S. claim format. Further, the claims submitted with this application to be prosecuted, and which are amended herein, reflect those claims as amended in the International Application and attached as annexes to the International Preliminary Examination Report (IPER). No new matter has been added. Prosecution on the merits hereof is respectfully requested.

Respectfully submitted,

Date: May 3, 2005

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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Serial No. :

Filing Date : Herewith

Examiner :

Group Art Unit:

Title : MULTILAYERED TRANSMUCOSAL THERAPEUTIC  
SYSTEM (as amended herein)

Attorney File : RO4037US (#90568)

Mail Stop PCT  
Commissioner for Patents  
P.O. Box 1450  
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**MARKED-UP SUBSTITUTE SPECIFICATION**

# MULTI-LAYER TRANSMUCOSAL THERAPEUTIC SYSTEM

## BACKGROUND OF THE INVENTION

### Cross-Reference to Related Applications

[00001] This application is a National Stage application of International Application No. PCT/EP03/012272, filed on November 4, 2003, which claims priority of German application number 102 52 726.1, filed on November 13, 2002.

### Field of the Invention

[00002] The invention relates to a multilayered film-shaped therapeutic system for transmucosal administration of active substances, especially of medicinal substances. These systems are suitable for rapid delivery of active substances over a prolonged period in a controlled manner.

### Description of the Prior Art

[00003] Mucoadhesive medicament forms are known in the state of the art for example in the form of mucoadhesive tablets, disks or film-shaped administration forms. Some of those medicament forms are already available on the market. Mucoadhesive medicament forms are applied to the mucosa, especially to the oral mucosa (buccal and/or gingival mucosa), thereby enabling the delivery of the active substance contained therein and absorption via the mucosa. It is ~~of advantage~~ advantageous here that the active substances enter the circulation quickly and a quick onset of action can be achieved. Medicament forms of this kind are suitable, in particular, for administering such active substances ~~[[as]]~~ that are ~~[[only]]~~ poorly absorbed ~~[[from]]~~ by the gastrointestinal tract and/or exhibit a short plasma half-life.

[00004] The best known mucoadhesive administration forms are tablets which are configured in two layers and consist of a mucoadhesive layer and a retarding backing layer (~~[[Aftab]]~~ AFTAB®, Rottapharm). There have been endeavours to improve the functional capability of such mucoadhesive tablets, for example by providing drainage notches which ~~[[are to]]~~ enable ~~[[that]]~~ saliva liquid ~~[[is]]~~ to be transported away from the application site. Such tablet systems are indeed capable of fulfilling their function, but they are experienced as unpleasant to the patients since they are relatively thick, hard and inflexible, and thereby induce a marked foreign body sensation.

[00005] Apart from the above, mucoadhesive "disks" are known which can be formulated on the basis of lipophile, insoluble polymer matrices and

hydrophile mucoadhesive polymers and, if required, surfactants. These disks usually have a thickness of approx. 1 mm and therefore cause an unpleasant foreign body-sensation in the mouth.

[00006] From US Patent No. 4 713 243 there are known mono- or multilayered mucoadhesive films whose mucoadhesive layer consists of hydroxypropyl cellulose, an ethylene oxide homopolymer, a water-insoluble polymer (e.g. ethyl cellulose, propyl cellulose, polyethylene, polypropylene) and a plasticizer. These administration forms are considered more pleasant by the patients, but their usefulness is highly restricted on account of the only short period of adhesion. This short duration of adhesion is due to the fact that the polymers employed are readily soluble in water, so that no appreciable retardation of adhesion does occur. To achieve that the mentioned mucoadhesive films adhere to the mucosa for a prolonged period of time, the content of water-insoluble polymer components (e.g. ethyl cellulose, propyl cellulose) in the formulation must be increased. However, as a consequence, the mucoadhesive systems thus produced have a greater thickness, which increases the foreign body sensation during the period of application. In addition, the greater thickness entails a decrease in the release of active substance since the diffusion paths become longer and the diffusion coefficients diminish.

[00007] It has also been proposed (Patent No. US 5 719 197) to improve the coherence of mucoadhesive systems by using clay as an additive. However, such clays must be regarded as disadvantageous because of their property of adsorbing certain active substances or of affecting the active substance stability by catalytic effects. Furthermore, the weight and thickness of the system is markedly increased by these additives.

[00008] The task underlying the present invention was thereby to provide mucoadhesive administration forms which do not have the above-mentioned disadvantages, in particular inducement of a foreign body sensation, insufficient active substance release and too short a duration of adhesion.

[00009] Furthermore, these mucoadhesive medicament forms are to enable a quick onset of action on the one hand and on the other hand, enable a continuous and controlled active substance delivery over a prolonged period of time.

### SUMMARY OF THE INVENTION

[000010] This task is surprisingly solved, ~~surprisingly~~, by film-shaped, at least double-layered transmucosal therapeutic systems according to ~~claim 1~~ the present invention and ~~[[by]] the preferred alternative embodiments of the present invention described in the dependent claims.~~

[000011] ~~According to claim 1, the~~ The inventive therapeutic systems which are suitable, in particular, for transmucosal administration of active substances have a structure of at least two layers which are connected with each other. At least one of these layers contains active substance. One of the two sides of the inventive system is limited by a mucoadhesive layer which optionally contains active substance or is free of active substance. During application, this mucoadhesive layer is in contact with the absorbing mucosa, e.g. oral mucosa. The mucoadhesive layer of the system is connected with a backing layer which is mono-layered or double-layered and which may serve as an active substance reservoir. A special property of the mucoadhesive layer consists in the fact that it is capable of swelling in aqueous media, but is insoluble or only poorly, i.e. slowly, soluble therein. The insolubility or reduced solubility increases the period of adhesion to the mucosa, thereby enabling an active substance release that lasts for a prolonged period of time. Since the inventive systems are film-shaped and may preferably have a thickness of less than 1 mm, they do not cause a foreign body sensation and are not ~~felt to be~~ unpleasant ~~[[by]]~~ to the patients~~[[,]].~~ whereby Therefore, the acceptance of such medicament forms is improved.

### BRIEF DESCRIPTION OF THE DRAWINGS

[000012] Figure 1 is a schematic cross-section view of the structure of layers of a first embodiment of the mucoadhesive system according to the present invention.

[000013] Figure 2 is a schematic cross-section view of the structure of layers of a second embodiment of the mucoadhesive system according to the present invention.

### DETAILED DESCRIPTION OF THE INVENTION

[000014] ~~[[The]]~~ It should be appreciated that the term "aqueous media" is ~~understood to mean~~ means, besides in addition to water, ~~in particular~~ physiological liquids, ~~especially~~ such as saliva.

[000015] Referring to Fig. 1 a system 1 is provided as a double-layered structure comprising a mucoadhesive layer or adhesive layer 2 and a backing layer or reservoir layer 3 connected to said mucoadhesive layer or adhesive layer 2. Mucoadhesive layer 2 of system 1 is in adhesive contact with a mucosa 4; status during application.

[000016] Turning now to Fig. 2, system 1 is provided as a three-layered structure comprising a mucoadhesive layer 2 and a backing layer 3. Backing layer 3 consists of two individual reservoir layers 3a, 3b. Reservoir layer 3a is a middle layer 3a and reservoir layer 3b is an outer layer or boundary layer 3b. The reservoir layer 3b, closing the system towards the outside, is configured so as to be diffusion-controlled.

[000017] The mucoadhesive layer 2 consists mainly of a polymer mixture which is film-forming, swellable in aqueous media but non-soluble or only poorly soluble therein. The polymer mixture comprises at least one hydrophile, mucoadhesive polymer embedded or dispersed in a polymer matrix. Optionally, the mucoadhesive layer 2 may contain active substance(s) or additives.

[000018] The aforementioned hydrophile polymer, respectively the hydrophile polymers is/are ~~preferably~~ selected from the group comprising hydrophile adhesive polymers carrying carboxyl groups, polyacrylates or polyacrylic acid derivatives (e.g. ~~Carbopol~~ CARBOPOL® types, from the firm of B.F. Goodrich) and their salts, carboxymethyl cellulose and its salts, poly(methyl vinyl ether maleic anhydride) and its aqueous or alcoholic hydrolysates and salts (e.g. ~~Gantrez~~ GANTREZ® types, such as ~~Gantrez~~ GANTREZ -AN, -S, -ES, -MS; from ISP).

[000019] The above-mentioned polymer matrix of the mucoadhesive layer is essentially based on polymers which are ~~hydrophile~~ hydrophilic, but insoluble or slowly soluble in an aqueous media. This polymer or these polymers is/are ~~preferably~~ selected from the group of polyvinyl alcohols and polyacrylates. Other polymers known to those skilled in the art which enable an anchorage of the mucoadhesive layer 2 on the adjacent backing layer 3 that is durable in dry condition or in aqueous environment, may also be utilized.

[000020] To ensure a durable connection between the mucoadhesive layer 2 and the backing layer 3 superimposed thereon (respectively one of the

individual layers 3a, 3b of the backing layer 3, in the case of a multi-layered backing layer) it is advantageous to select base polymers which are identical with those polymers employed for preparing the backing layer 3, or are at least chemically allied thereto.

[000021] ~~It is generally preferred for neighbouring~~ Neighbouring layers of the film-shaped system ~~[[to]]~~ contain one or more identical or chemically allied base polymers which are ~~preferably~~ selected from the group of the polyacrylates.

[000022] In this way it can be ensured that for the period of application the mucoadhesive layer 2 remains durably connected with the backing layer 3, even in aqueous environment (oral cavity).

[000023] According to ~~a preferred one~~ embodiment of the present invention, the polymers of the mucoadhesive layer 2 are crosslinked by employing physical or/and chemical methods. By cross-linking, the degree of solubility can be reduced without affecting hydrophilicity. In this way it is possible to additionally, and with particular advantage, further improve the duration of adhesion to the mucosa 4. Suitable crosslinking reagents and crosslinking processes are known to those skilled in the art (e.g. use of aluminium acetylacetonate or titanyl acetylacetonate as crosslinking agent).

[000024] The mucoadhesive layer 2 may contain additives suitable for modulating the adhesive properties~~[[,]]~~. It should be appreciated that these are known to those skilled in the art.

[000025] The backing layer 3 or (in the case of a multilayer backing layer) the individual layers 3a, 3b of the backing layer 3 is/are ~~preferably~~ produced on the basis of polyacrylates, especially on the basis of neutralised polymethyl methacrylates (e.g. ~~Eudragit~~ EUDRAGIT® E 100, ~~Eudragit~~ EUDRAGIT® NE 30 D, ~~Plastoid~~ PLASTOID® B; Röhm Pharma). ~~Especially preferred~~ are For example, polyacrylates which are capable of swelling in aqueous media – largely independently of the pH value -, but are not soluble therein may be employed. The backing layer 3 or at least one of the layers 3a, 3b forming the backing layer 3 may optionally contain one or more auxiliary substances, ~~preferably~~ for example selected from the group of the plasticizers, penetration enhancers, solubilizers, colorants, pigments and matrix formers. ~~Suitable~~ It should be appreciated that suitable substances are known to those skilled in the art.

**[000026]** Suitable as plasticizers are, for instance, plasticizers from the group comprising hydrocarbons, alcohols (especially higher alcohols such as dodecanol, undecanol, octanol), polyhydric alcohols, polyethylene glycols, triglycerides, carboxylic acids, derivatives of carboxylic acids, ethers, esters (e.g. diethyl phthalate, n-butyl adipate, citric acid esters) und amines.

**[000027]** Suitable as absorption or permeation enhancers are, in particular, substances selected from the group comprising the following substances and substance classes: saturated or unsaturated fatty acids, fatty acid esters, especially esters with methanol, ethanol or isopropanol (e.g. oleic acid ethyl ester, oleic acid methyl ester, lauric acid methyl ester, lauric acid ethyl ester, adipic acid methyl ester, adipic acid ethyl ester), straight-chain or branched fatty alcohols and esters thereof, especially esters with acetic acid or lactic acid (e.g. ethyl oleate, ethyl laurate, ethyl palmitate, ethyl lactate, propyl lactate, propyl palmitate, propyl laurate, propyl oleate), polyhydric aliphatic alcohols or polyethylene glycols, sorbitan fatty acid esters and their derivatives obtained by ethoxylation, fatty alcohol ethoxylates, polyoxyethylene fatty acid ester; lauric acid diethanolamide, oleic acid diethanolamide, coconut fatty acid diethanolamide, D-alpha-tocopherol, lauric acid hexyl ester, 2-octyldodecanol, dexpanthenol, isopropylidene glycerol, transcutol (= diethylene glycol monoethyl ether), DEET (= N,N-diethyl-m-tolueneamide), solketal, ethanol, 1,2-propanediol or other short-chain alcohols (e.g. alcohols with up to 6 C atoms), as well as menthol and other essential oils or components of essential oils. To optimize active substance flow, it is also possible to use combinations of two or more enhancers.

**[000028]** The total constituent amount of plasticizers and permeation-enhancing substances may be up to 10%-wt, relative to the film-shaped medicament form. ~~Particularly preferred is~~ Having a content of less than 5%-wt., especially less than 1%-wt. may also be employed.

**[000029]** Examples for solubilizers are polyhydric alcohols such as 1,2-propanediol, butanediol, glycerol, polyethylene glycol 400, tetrahydrofurfuryl alcohol, diethylene glycol monoethyl ether, diethyl toluamide and monoisopropylidene glycerol. The portion of the solubilizers(s), relative to a medicament form, can be between 0.1 and 10%-wt, preferably or even 0.5 to 5%-wt.



[000030] Suitable as pigments are, in particular, talcum, titanium dioxide, iron oxide or lamellar pigments. The pigment portion can amount to up to 80, preferably or even up to 70%-wt, relative to the polymer portion in the respective layer.

[000031] [[The]] As shown in Fig. 1, the inventive film-shaped mucoadhesive systems are constructed, in the simplest case, of two layers, namely a mucoadhesive layer 2 and a backing layer 3 connected ~~therewith, which to~~ said backing layer 3. Backing layer 3 may serve as an active substance reservoir (~~Fig. 1~~). In addition, the mucoadhesive layer 2 may also contain active substance, ~~preferably~~ such as the same active substance as contained in the backing layer 3.

[000032] The active substance release from the system 1 to the mucosa 4 takes places by diffusion from the layers of the system 1.

[000033] According to ~~a preferred~~ one embodiment of the present invention, the backing layer 3 is modified by suitable additives in such a manner that the permeation of water and the diffusion of active substance in [[this]] backing layer 3 is reduced or blocked, relative to the diffusion and permeation in the mucoadhesive layer 2.

[000034] In further embodiments of the invention, ~~it is provided for~~ the systems may [[to]] be designed as multilayer systems and ~~preferably to~~ can contain up to 6 individual layers, such as with a layer number of 2 to 4 ~~being preferred~~. In each case, one of the surfaces of the system is formed by a mucoadhesive layer 2. ~~Preferably, all~~ All of the layers may contain the same active substance, at the same or different concentrations.

[000035] The multilayered structure enables the manufacture of inventive systems which immediately after application release an initial burst dose and subsequently release a maintenance dose at a reduced delivery rate over a prolonged period of time (several hours, preferably 0.5 to 24 hours).

[000036] Especially advantageous are embodiments wherein the backing layer 3 is constructed of two or more individual layers 3a, 3b which are superimposed one upon another and are connected with one another. In this way it is possible to increase the active substance dose contained in the system 1. In addition, the individual layers may contain additives which modify the solubility and the diffusion coefficient of the active substance in the respective layer. Thereby, a multilayer is obtained which has a defined

concentration gradient. This embodiment is particularly advantageous. The formation of a concentration gradient can, in addition, be assisted by providing the active substance in the individual layers in increasing or decreasing amounts or concentrations.

[000037] According to ~~a further preferred~~ an additional embodiment of the present invention, it is provided that the backing layer 3 or that outer layer which is located on the side of the system that is opposite the mucoadhesive layer 2 and ~~[[there]]~~ forms the outer surface, is modified by suitable additives such that the permeation of water and the diffusion of active substance in this layer is reduced or blocked, relative to the diffusion and permeation in the mucoadhesive layer 2 or in the other layers of the backing layer 3.

[000038] In this manner, a transmucosal system 1 is obtained which has a structure of at least three layers, namely comprising a mucoadhesive layer 2, at least one middle reservoir layer 3a connected ~~thereto~~ to said mucoadhesive layer 2, and an outer layer or boundary layer 3b connected ~~[[with]]~~ to said reservoir layer 2 (Fig. 2). In the latter layer, the diffusion of active substance – relative to the middle layer(s) – is reduced or even completely blocked.

[000039] The modification of the diffusion and permeation properties can be brought about, in particular, by varying the pigment content or/and by admixing suitable diffusion-retarding polymeric (e.g. ethyl cellulose, propyl cellulose) or non-polymeric auxiliary substances. In this manner, it is possible to adjust the diffusion properties of the backing layer 3, respectively the outermost layer 3b of the backing layer 3, between two extremes, namely between complete blockage of the diffusion on the one hand, and practically unimpeded or unmodified active substance diffusion from the matrix. Thus it is possible to optionally manufacture systems which release the active substance(s) on one side (i.e. only on the mucoadhesive side) or on two sides (i.e. on the mucoadhesive side and on that side of the system which is opposite thereto).

[000040] At least the middle layer(s) 3a of the system contain(s) the active substance, ~~preferably, also the aforementioned outer~~ Outer boundary layer 3b ~~contains~~ may contain the same active substance(s). In addition, the mucoadhesive layer 2 may also contain an active substance.

[000041] With the above described, at least three-layered structure comprising the ~~[[said]]~~ outer layer 3b, a system 1 is obtained wherein the delivery of active substance is controlled by a combination of matrix-controlled diffusion and membrane-controlled release.

[000042] Generally such a system, which is based on a mixed control (combination of matrix and membrane control) would release the active substance in a kind of saturation function, i.e. the delivery rate of the system would decrease further and further as the exhaustion of the system increases. By a suitable formulation, especially by a suitable selection of the matrix polymer(s) (increasing the portion of hydrophile functional groups), or by adding suitable hydrophile, water-binding additives (especially polyalcohols or polymeric surfactants with high HLB value, ~~preferably~~ such as  $HLB \geq 10$ , ~~especially or even~~  $HLB \geq 15$ ), it is possible to influence and increase the degree of water uptake or the degree of swelling of the reservoir layer with increasing retention time of the system in the moist medium (i.e. at the application site in the oral cavity).

[000043] By ~~means of~~ the above-described measures, the diffusion coefficient in the reservoir layer 3 can be increased by an increase in the swelling or by an increase in the degree of hydration. It is thereby possible to compensate the decrease in the release rate, caused by the decrease of the concentration gradient, by an increase in the swelling and hydration of the active substance matrix such that a release results which is essentially linear, this is accompanied by a high exhaustion of the system.

[000044] These properties of the systems according to the invention are of significance especially with a view to a prolonged application of the system, for instance over a period of several hours (e.g. 2 to 24 h). This is true, in particular, where the substances to be administered have a correspondingly narrow therapeutic window.

[000045] At least one of the layers of the inventive film-shaped systems 1 contains an active substance or a combination of active substances. The polymers of the individual layers form a polymer matrix which may serve as an active substance reservoir. In this polymer matrix the active substance(s) are already contained, in dissolved, suspended or emulsified form, ~~preferably~~ whereby "dissolved" is in the sense of a "solid solution". Suitable as active substances are, in particular, medicinal substances, ~~with~~

~~particular preference~~ such as highly efficacious medicinal substances, e.g. from the following groups: agents acting on the nervous system, psychopharmacological agents, sedatives, narcotics, hormones, insulin-like active agents, analgesics, anticonvulsives, anti-parkinson agents, medicaments acting on the cardiovascular system, anti-infectives, active agents for treating metabolic disturbances (e.g. lipid-lowering agents), agents acting on the muscular system, and others.

[000046] The inventive systems are suitable above all for administering medicaments that are subject to rapid metabolism or/and are absorbed only insufficiently via the gastrointestinal route.

[000047] The invention ~~will be~~ is further explained ~~in more detail~~ in the following ~~by means of examples and drawings.~~

~~Fig. 1 and Fig. 2 show, in schematic cross section, the structure of layers of two examples of mucoadhesive systems (1) according to the invention.~~

~~Fig. 1 shows a system (1) with a double-layered structure comprising a mucoadhesive layer or adhesive layer (2) and a backing layer or reservoir layer (3) connected therewith. The mucoadhesive layer (2) of the system (1) represented is in adhesive contact with a mucosa (4); status during application.~~

~~Fig. 2 shows a system (1) with a three-layered structure comprising a mucoadhesive layer (2) and a backing layer (3), which backing layer (3) consists of two individual reservoir layers (3a, 3b), namely a middle layer (3a) and an outer layer or boundary layer (3b). The reservoir layer (3b), closing the system towards the outside, is preferably configured so as to be diffusion-controlled.~~

[000048] Example:

[000049] Preparation of a three-layered system (as in Fig. 2)

[000050] An active substance is dissolved in a neutral polyacrylate (e.g. ~~Eudragit~~ EUDRAGIT<sup>®</sup> NE 30 D; Röhm), either directly or employing a suitable solvent known to those skilled in the art, if need be by using a dissolving intermediary or solubilizer. The selection of the suitable method is dependent on the solubility, respectively the dissolving properties of the active agent employed.

[000051] Furthermore, an appropriate pigment is added to the active substance-containing polymer solution, e.g. talcum, TiO<sub>2</sub>, iron oxide or lamellar

pigments, and a homogenous liquid is prepared. The pigment content is relatively high and is at approx. 60%-wt, relative to the polymer portion.

[000052] Subsequently, the viscosity of the liquid is adjusted such that it is suitable for the subsequent processing steps. The liquid is applied, preferably by means of a casting method or spraying method[[,]] to an inert support and is subjected to subsequent drying[[,]] which results in a thin film. The inert support employed must be such that the film remains adhering thereto after drying, but can be detached from the support without being destroyed.

[000053] In the same manner as above-described, a second liquid is prepared which differs from the first formulation only in that it does not contain the pigment or contains a lower portion of pigment. Thereby, the active substance content is increased relative to the entire solids content, as compared to the liquid prepared first. The second liquid is coated, again by means of a spraying or casting method, onto the layer prepared first and is subsequently dried so that a two-layer laminate with two reservoir layers is obtained.

[000054] To prepare the mucoadhesive layer, an aqueous solution of highly ~~hydrolysed~~ hydrolyzed polyvinyl alcohol (e.g. ~~Mowiol~~ MOWIOL® 28-99, Clariant) of suitable concentration (e.g. 10%-wt.; optionally 0.5 to 60%-wt) is prepared, and a suitable portion of adhesive polymer (e.g. ~~Gantrez~~ GANTREZ® S 95; ISP) is dissolved therein. The portion of adhesive polymer in this example corresponds to the polyvinyl alcohol portion (that is, mixing ratio 1:1; weight content). But other mixing ratios can be employed as well, e.g. in the range of 50:1 to 1:50, relative to the portion of adhesive : the portion of polyvinyl alcohol).

[000055] The resultant homogenous solution is coated, again employing a suitable application method, onto the previously prepared two-layer laminate, and subsequently dried.

[000056] This yields a three-layer laminate which – depending on the coating weight – is approx. 50 to 250 µm in thickness. The top side of this laminate has good tackiness in moist state and has mucoadhesive properties. The laminate as a whole has very good flexibility and adheres to a mucosa for several hours after application thereof.

[000057] The inventive transmucosal systems are advantageously suitable for administering active agents, especially medicaments, for therapeutic or prophylactic treatment in human or veterinary medicine.

[000058] What has been described above are preferred aspects of the present invention. It is of course not possible to describe every conceivable combination of components or methodologies for purposes of describing the present invention, but one of ordinary skill in the art will recognize that many further combinations and permutations of the present invention are possible. Accordingly, the present invention is intended to embrace all such alterations, combinations, modifications, and variations that fall within the spirit and scope of the appended claims.